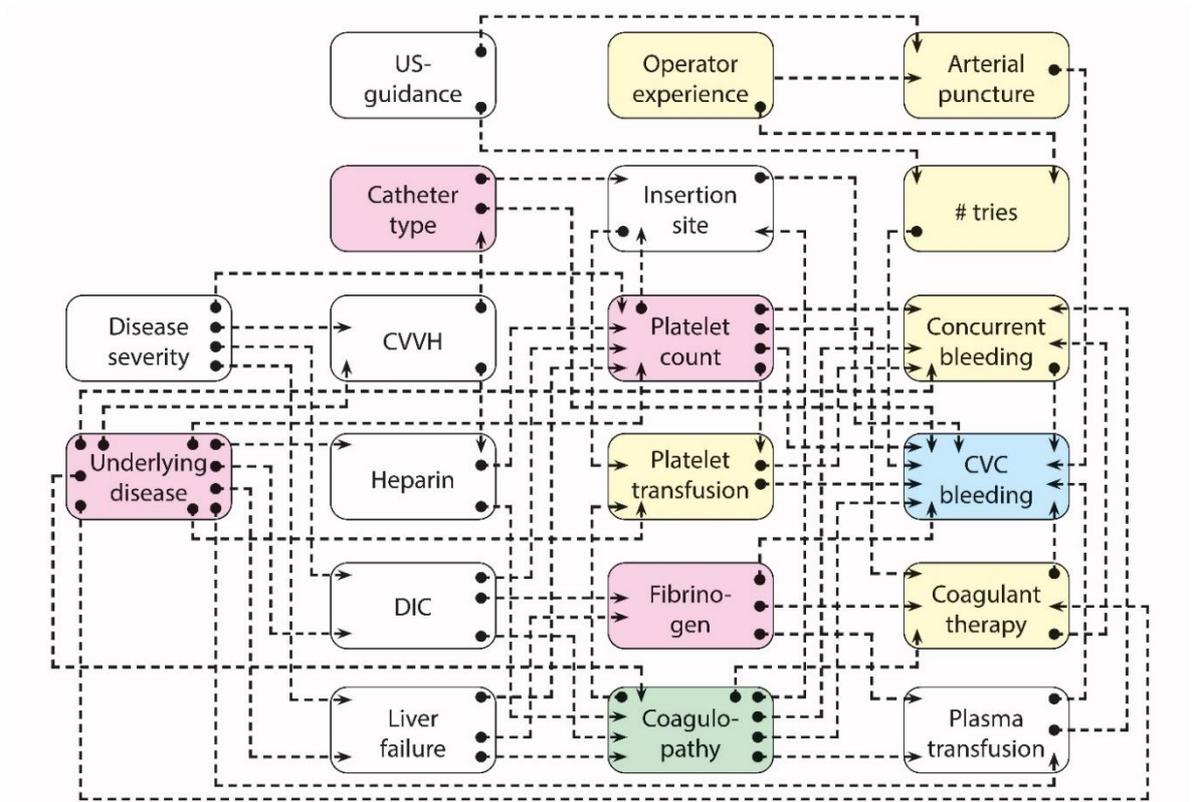


Appendix 1. Interrater reliability for assessing CVC-related bleeding

		Rater 2			
		Grade 0	Grade 1	Grade 2	Grade 3
Rater 1	Grade 0	238	17	1	0
	Grade 1	11	15	0	1
	Grade 2	3	2	3	0
	Grade 3	0	0	1	1

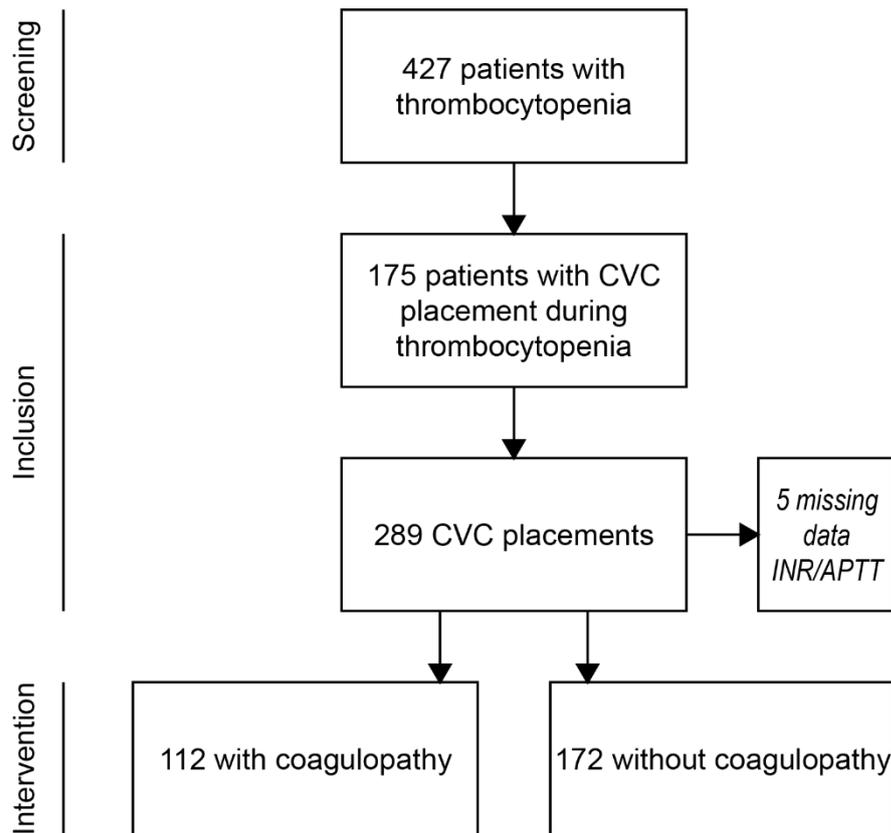
CVC = Central venous catheter | Cohen's κ = 0,481

Appendix 2. Directed acyclic graph



Directed acyclic graph (DAG) representing a theoretical framework of the relation between coagulopathy, CVC bleeding and their confounders. Green = predictor; Blue = Outcome; Red = Definite confounder (based on DAG); Yellow = Possible confounder (based on univariable analysis)

Appendix 3. Study flow



CVC = Central venous catheter; INR = International normalized ratio; APTT = Activated partial thromboplastin time

Appendix 4. Number of CVC placements per patient

	Total	Abnormal coagulation	Normal coagulation
N (CVCs)	289	112	172
N (patients)	175	79	111
Number of CVCs per patient, n(%)			
1	106 (60.6)	52 (65.8)	73 (65.8)
2	45 (25.7)	22 (27.8)	26 (23.4)
3	14 (8.0)	4 (5.1)	7 (6.3)
>3	10 (5.7)	1 (1.3)	5 (4.5)

CVC = Central venous catheter | There is an overlap of 15 patients between the normal and abnormal coagulation groups, who underwent CVC placement both with and without coagulopathy.

Appendix 5. Baseline characteristics (full)

	Total	Normal coagulation	Abnormal coagulation	Statistical significance
N	289	172	112	
Patient demographics				
Female, n(%)	121 (41.9)	78 (45.3)	39 (34.8)	
Age (years), median (IQR)	57 (43-64)	58 (51-63)	53 (39-64)	
BMI (kg/m ²), median (IQR)	25 (22-30)	26 (23-30)	25 (22-29)	
Disease severity				
SOFA-score, mean (SD)	12.8 (4.3)	11.6 (4.2)	14.5 (4.0)	***
CP-score, median (IQR)	9 (7-10)	7 (7-9)	10 (8-11)	***
CCI, median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	
ISTH DIC-score, median (IQR)	7 (6-7)	7 (5-7)	7 (7-7)	***
Temperature (°C), mean(SD)	37.2 (1.2)	37.3 (1.1)	37.0 (1.3)	
Concurrent bleeding elsewhere, n(%)	151 (52.2)	87 (50.6)	62 (55.4)	
Laboratory values				
Platelets (x 10 ⁹ /L) , median (IQR)	27 (16-38)	27 (15-38)	26 (17-36)	
Hemoglobin (mmol/L), median (IQR)	5.1 (4.6-5.9)	5.1 (4.6-5.7)	5.1 (4.6-6.0)	
INR, median (IQR)	1.3 (1.1-1.6)	1.2 (1.1-1.3)	1.7 (1.5-2.2)	***
aPTT (sec) , median (IQR)	35 (29-46)	31 (28-36)	50 (40-61)	***
Fibrinogen (g/L), median (IQR)	3.4 (1.8-5.5)	4.2 (2.7-6.4)	2.0 (1.3-3.7)	***
D-dimer (g/L), median (IQR)	9.8 (3.5-20.5)	10.0 (3.2-18.5)	9.5 (5.8-23.5)	
Diagnoses				
ICU admission diagnosis, n(%)				
Sepsis	132 (45.7)	80 (46.5)	48 (42.9)	
Pulmonary	54 (18.7)	34 (19.8)	19 (17.0)	
Cardiac	13 (4.5)	3 (1.7)	10 (8.9)	
Routine post-cardiac surgery	15 (5.2)	11 (6.4)	4 (3.6)	
Surgery (other)	28 (9.7)	14 (8.1)	14 (12.5)	
Other	47 (16.3)	30 (17.4)	17 (15.2)	
Haematological diagnosis, n(%)				
Any	149 (51.6)	105 (61.0)	40 (35.7)	
AML	47 (16.3)	33 (19.2)	13 (11.6)	
ALL	18 (6.2)	13 (7.6)	5 (4.5)	
Lymphoma	40 (13.8)	28 (16.3)	11 (9.8)	
Multiple myeloma	10 (3.5)	3 (1.7)	5 (4.5)	
MDS	12 (4.2)	10 (5.8)	2 (1.8)	
Other	22 (7.6)	18 (10.5)	4 (3.6)	
CVC placement				
US-guided, n(%)	212 (99.5)	134 (99.3)	76 (100.0)	
Number of tries, median (iqr)	1 (1-1)	1 (1-1)	1 (1-2)	
CVVH catheter, n(%)	113 (39.4)	58 (34.1)	55 (49.1)	*
Number of lumens, median (iqr)	3 (2-3)	3 (2-3)	3 (2-3)	
Insertion site, n(%)				
Internal jugular vein	167 (58.2)	109 (64.1)	54 (48.2)	
Subclavian vein	8 (2.8)	5 (2.9)	3 (2.7)	
Femoral vein	112 (39.0)	56 (32.9)	55 (49.1)	

Operator specialty, n(%)			
Anaesthesiology	123 (64.4)	76 (63.3)	47 (68.1)
Internal medicine	32 (16.8)	22 (18.3)	9 (13.0)
Neurology	16 (8.4)	10 (8.3)	6 (8.7)
Cardiology	10 (5.2)	5 (4.2)	4 (5.8)
Other	10 (5.2)	7 (5.8)	3 (4.3)
Concurrent therapies^a			
Unfractionated heparin, n(%)	17 (5.9)	8 (4.7)	9 (8.0)
Low molecular weight heparin, n(%)			
None	104 (36.1)	59 (34.3)	41 (36.9)
Normal prophylactic dose	169 (58.7)	107 (62.2)	61 (55.0)
Double prophylactic dose	8 (2.8)	2 (1.2)	6 (5.5)
Therapeutic dose	7 (2.4)	4 (2.3)	3 (2.7)
Coumarin or DOAC, n(%)	6 (2.1)	3 (1.7)	2 (1.8)
Platelet aggregation inhibitor, n(%)	16 (5.5)	9 (5.2)	7 (6.2)
Tranexemic acid, n(%)	50 (17.3)	31 (18.0)	19 (17.0)
Clotting factors, n(%)	41 (14.2)	19 (11.0)	22 (19.6)
Vitamin K, n(%)	32 (11.1)	14 (8.1)	18 (16.1)
Platelet transfusion, n(%)	117 (40.5)	73 (42.4)	43 (38.4)
Plasma transfusion, n(%)	8 (2.8)	1 (0.7)	7 (6.5)

BMI = Body Mass Index; SOFA = Sequential Organ Failure Assessment; CP = Child-Pugh; CCI = Charlson Comorbidity Index; ISTH = International Society on Thrombosis and Haemostasis; DIC = Disseminated intravascular coagulation; INR = International Normalised Ratio; aPTT = activated Partial Thromboplastin Time; ICU = Intensive Care Unit; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoid leukemia; MDS = Myelodysplastic Syndrome; CVC = Central Venous Catheter; US = ultrasound; CVVH = Continuous Venovenous Hemofiltration; DOAC = Direct Oral Anticoagulants | * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ | ^a Unfractionated heparin was not counted if it was stopped >1 hour prior to CVC placement, other (anti-) coagulants were counted if administered <1 week prior to CVC placement

Appendix 6. Baseline characteristics after inverse probability of treatment weighting

	Total	No coagulopathy	Coagulopathy	
N	280	172	108	
Patient demographics				
Female, n(%)	123 (44.0)	79 (45.9)	44 (40.9)	
Age (years), median (iqr)	57 (43-63)	58 (51-63)	52 (39-63)	
BMI (kg/m ²), median (iqr)	25 (22-30)	26 (22-30)	24 (22-29)	
Disease severity				
SOFA-score, mean (sd)	12.6 (4.2)	12.0 (4.3)	13.4 (4.0)	*
CP-score, median (iqr)	9 (7-10)	8 (7-9)	9 (8-11)	***
CCI, median (iqr)	3 (2-5)	3 (2-5)	3 (2-5)	
ISTH DIC-score, median (iqr)	7 (6-7)	6 (5-7)	7 (7-7)	**
Temperature (°C), mean(sd)	37.1 (1.2)	37.2 (1.1)	37.1 (1.3)	
Concurrent bleeding elsewhere, n(%)	144 (51.4)	88 (51.4)	56 (51.4)	
Laboratory values				
Platelets (x 10 ⁹ /L) , median (iqr)	25 (15-38)	25 (15-38)	25 (16-36)	
Hemoglobin (mmol/L), median (iqr)	5.0 (4.6-5.9)	5.0 (4.6-5.7)	5.0 (4.4-6.1)	
INR, median (iqr)	1.3 (1.1-1.5)	1.2 (1.1-1.3)	1.6 (1.5-2.1)	***
aPTT (sec) , median (iqr)	35 (29-44)	31 (28-38)	47 (37-59)	***
Fibrinogen (g/L), median (iqr)	3.4 (1.9-5.7)	3.4 (2.0-5.5)	3.3 (1.6-6.1)	
D-dimer (g/L), median (iqr)	10.5 (5.3-21.6)	13.1 (5.3-21.4)	8.7 (4.8-21.6)	
Diagnoses				
ICU admission diagnosis, n(%)				
Sepsis	126 (44.9)	77 (44.9)	49 (44.9)	
Pulmonary	57 (20.2)	36 (20.7)	21 (19.4)	
Cardiac	11 (4.0)	6 (3.5)	5 (4.7)	
Routine post-cardiac surgery	12 (4.4)	9 (5.1)	4 (3.3)	
Surgery (other)	26 (9.2)	16 (9.0)	10 (9.4)	
Other	49 (17.3)	29 (16.9)	20 (18.2)	
Haematological diagnosis, n(%)				
Any	141 (50.2)	89 (51.6)	52 (47.9)	
AML	41 (14.6)	27 (15.5)	14 (13.3)	
ALL	19 (6.6)	11 (6.4)	8 (7.0)	
Lymphoma	41 (14.7)	24 (13.8)	18 (16.2)	
Multiple myeloma	11 (3.8)	7 (4.2)	3 (3.2)	
MDS	12 (4.1)	7 (4.2)	4 (4.0)	
Other	18 (6.3)	13 (7.5)	5 (4.3)	
CVC placement				
US-guided, n(%)	210 (99.6)	136 (99.5)	74 (100.0)	
Number of tries, median (iqr)	1 (1-1)	1 (1-1)	1 (1-2)	
CVVH catheter, n(%)	115 (41.3)	68 (39.9)	47 (43.7)	
Number of lumens, median (iqr)	3 (2-3)	3 (2-3)	3 (2-3)	
Insertion site, n(%)				*
Internal jugular vein	155 (55.8)	106 (62.6)	49 (45.2)	
Subclavian vein	10 (3.5)	7 (3.8)	3 (2.9)	
Femoral vein	113 (40.7)	57 (33.6)	56 (51.8)	
Operator specialty, n(%)				
Anaesthesiology	128 (67.2)	80 (65.5)	48 (70.4)	

Internal medicine	27 (14.0)	17 (14.2)	9 (13.6)
Neurology	15 (7.7)	11 (8.7)	4 (5.9)
Cardiology	11 (5.9)	7 (5.6)	4 (6.4)
Other	10 (5.2)	7 (6.1)	3 (3.6)
Concurrent therapies†			
Unfractionated heparin, n(%)	17 (6.2)	10 (5.6)	8 (7.3)
Low molecular weight heparin, n(%)			
None	102 (36.6)	63 (36.5)	40 (36.8)
Normal prophylactic dose	161 (57.5)	104 (60.6)	57 (52.5)
Double prophylactic dose	8 (2.8)	2 (1.0)	6 (5.5)
Therapeutic dose	9 (3.1)	3 (1.8)	6 (5.2)
Coumarin or DOAC, n(%)	3 (1.2)	2 (1.2)	1 (1.2)
Platelet aggregation inhibitor, n(%)	14 (4.8)	8 (4.7)	5 (4.9)
Tranexemic acid, n(%)	48 (17.1)	35 (20.1)	13 (12.3)
Clotting factors, n(%)	38 (13.5)	22 (12.9)	16 (14.5)
Vitamin K, n(%)	27 (9.7)	16 (9.0)	12 (10.9)

*BMI = Body Mass Index; SOFA = Sequential Organ Failure Assessment; CP = Child-Pugh; CCI = Charlson Comorbidity Index; ISTH = International Society on Thrombosis and Haemostasis; DIC = Disseminated intravascular coagulation; INR = International Normalised Ratio; aPTT = activated Partial Thromboplastin Time; ICU = Intensive Care Unit; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoid leukemia; MDS = Myelodysplastic Syndrome; CVC = Central Venous Catheter; US = ultrasound; CVVH = Continuous Veno-Venous Hemofiltration; DOAC = Direct Oral Anticoagulants | * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ | † Unfractionated heparin was not counted if it was stopped >1 hour prior to CVC placement, other (anti-) coagulants were counted if administered <1 week prior to CVC placement*

Appendix 7. Standardised mean difference before and after IPTW

	Before IPTW	After IPTW
Platelet count	0.07	0.03
Fibrinogen	0.79	0.01
ICU admission diagnosis*	0.43	0.19
Haematological diagnosis*	0.61	0.18
Catheter type	0.31	0.08
Number of tries	0.10	0.03
Arterial puncture	0.20	0.11
Operator specialty*	0.18	0.17
Bleeding elsewhere	0.10	0.001
Clotting factors	0.24	0.04
Squared continuous variables		
Platelet count	0.14	0.07
Fibrinogen	0.66	0.12
Number of tries	0.08	0.08

*IPTW = Inverse Probability of Treatment Weighing; ICU = Intensive Care Unit | * Variables were multinomial*

Appendix 8. Percentages missing data

Variable	Number missing	Percentage missing
DIC score	152	52.6
D-dimer	139	48.1
Operator specialty	98	33.9
Child-Pugh score	94	32.5
Fibrinogen	92	31.8
Ultrasound guidance	76	26.3
Albumin	74	25.6
Hemoglobin (1h post CVC)	72	24.9
Arterial puncture	57	19.7
SOFA score	56	19.4
Number of tries	52	18.0
Bilirubin	47	16.3
Hemoglobin (24h post CVC)	34	11.8
Number of lumens	27	9.3
Height	22	7.6
Temperature	12	4.2
Hemoglobin (before CVC)	8	2.8
APTT	7	2.4
Weight	6	2.1
Encephalopathy	6	2.1
INR (worst within 24h)	5	1.7
Coagulopathy	5	1.7
Platelet count	4	1.4
CVC side	4	1.4
INR (most recent)	4	1.4
SOFA respiratory component	4	1.4
Glasgow coma scale	3	1.0
CVC site	2	0.7
CVC type	2	0.7
SOFA cardiovascular component	2	0.7
Creatinin	1	0.3
Charlson comorbidity score	1	0.3
LMWH	1	0.3

DIC = Disseminated intravascular coagulation; CVC = Central venous catheter; SOFA = Sequential organ failure assessment; APTT = Activated partial thromboplastin time; INR = International normalized ratio; LMWH = Low molecular weight heparin | Only variables with missing data are shown, remaining variables were complete

Appendix 9. Univariable analysis of post-CVC bleeding

	Total	Bleeding	Non-bleeding	
N	289	44	245	
Disease severity				
SOFA-score, mean (sd)	12.8 (3.4)	12.2 (4.6)	12.9 (4.3)	
CP-score, median (iqr)	9 (7-10)	9 (7-10)	9 (7-10)	
CCI, median (iqr)	3 (2-5)	4 (2-4)	3 (2-5)	
ISTH DIC-score, median (iqr)	7 (6-7)	7 (6-7)	7 (6-7)	
Concurrent bleeding elsewhere, n(%)	151 (52.2)	32 (72.7)	119 (48.6)	**
Laboratory values				
Platelets (x 10 ⁹ /L) , median (iqr)	27 (16-38)	25 (15-33)	27 (16-40)	
INR, median (iqr)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.2-1.5)	
aPTT (sec) , median (iqr)	35 (29-46)	35 (29-45)	35 (30-56)	
Fibrinogen (g/L), median (iqr)	3.4 (1.8-5.5)	2.0 (1.1-5.2)	3.5 (2.0-5.7)	*
Diagnoses				
ICU admission diagnosis, n(%)				
Sepsis	132 (45.7)	20 (45.5)	112 (45.7)	
Pulmonary	54 (18.7)	6 (13.6)	48 (19.6)	
Cardiac	13 (4.5)	1 (2.3)	12 (4.9)	
Routine post-cardiac surgery	15 (5.2)	1 (2.3)	14 (5.7)	
Surgery (other)	28 (9.7)	3 (6.8)	25 (10.2)	
Other	47 (16.2)	13 (29.6)	34 (13.9)	
Haematological diagnosis, n(%)				
Any	149 (51.6)	22 (50.0)	127 (51.8)	
AML	47 (18.7)	5 (11.4)	42 (17.1)	
ALL	18 (6.2)	2 (4.5)	16 (6.5)	
Lymphoma	40 (13.8)	6 (13.6)	34 (13.9)	
Multiple myeloma	10 (3.5)	2 (4.5)	8 (3.3)	
MDS	12 (4.2)	2 (4.5)	10 (4.1)	
Other	22 (7.6)	5 (11.4)	17 (6.9)	
CVC placement				
US-guided, n(%)	212 (99.5)	35 (97.2)	177 (100.0)	
Insertion site, n(%)				
Internal jugular vein	167 (58.2)	28 (63.6)	139 (57.2)	
Subclavian vein	8 (2.8)	1 (2.3)	7 (2.9)	
Femoral vein	112 (39.0)	15 (34.1)	97 (39.9)	
Number of tries, median (iqr)	1 (1-1)	1 (1-2)	1 (1-1)	*
Arterial puncture, n(%)	4 (1.7)	4 (10.5)	0 (0.0)	***
CVVH catheter, n(%)	113 (39.4)	12 (27.9)	101 (41.4)	#
Operator specialty, n(%)				
Anaesthesiology	123 (64.4)	24 (77.4)	99 (61.9)	
Internal medicine	32 (16.8)	4 (12.9)	28 (17.5)	
Neurology	16 (8.4)	0 (0.0)	16 (10.0)	
Cardiology	10 (5.2)	0 (0.0)	10 (6.2)	
Other	10 (5.2)	3 (9.7)	7 (4.4)	
Concurrent therapies†				
Platelet transfusion, n(%)	117 (40.5)	19 (43.2)	98 (40.0)	
Plasma transfusion, n(%)	8 (2.8)	2 (4.7)	6 (2.5)	

Unfractionated heparin, n(%)	17 (5.9)	4 (9.1)	13 (5.3)	
Low molecular weight heparin, n(%)				
None	104 (36.1)	14 (31.8)	90 (36.9)	
Normal prophylactic dose	169 (58.7)	26 (59.1)	143 (58.6)	
Double prophylactic dose	8 (2.8)	1 (2.3)	7 (2.9)	
Therapeutic dose	7 (2.4)	3 (6.8)	4 (1.6)	
Coumarin or DOAC, n(%)	6 (2.1)	1 (2.3)	5 (2.0)	
Platelet aggregation inhibitor, n(%)	16 (5.5)	3 (6.8)	13 (5.3)	
Tranexemic acid, n(%)	50 (17.3)	10 (22.7)	40 (16.3)	
Clotting factors, n(%)	41 (14.2)	10 (22.7)	31 (12.7)	#
Vitamin K, n(%)	32 (11.1)	5 (11.4)	27 (11.0)	

SOFA = Sequential Organ Failure Assessment; CP = Child-Pugh; CCI = Charlson Comorbidity Index; ISTH = International Society on Thrombosis and Haemostasis; DIC = Disseminated intravascular coagulation; ICU = Intensive Care Unit; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoid leukemia; MDS = Myelodysplastic Syndrome; CVC = Central Venous Catheter; US = ultrasound; CVVH = Continuous Veno-Venous Hemofiltration; DOAC = Direct Oral Anticoagulants | # $p < 0.2$ * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ | † Unfractionated heparin was not counted if it was stopped >1 hour prior to CVC placement, other (anti-) coagulants were counted if administered <1 week prior to CVC placement

Appendix 10. CVC related bleeding in cohorts of platelet count, INR and APTT

	No bleeding	Grade 1	Grade 2	Grade 3	Total
Overall	240 (84.5)	38 (13.4)	4 (1.4)	2 (0.7)	284
Platelet count (x10 ⁹ /L)					
41-50	51 (98.1)	1 (1.9)	-	-	52
31-40	42 (79.2)	11 (20.8)	-	-	53
21-30	49 (75.4)	14 (21.5)	1 (1.5)	1 (1.5)	65
11-20	60 (88.2)	6 (8.8)	1 (1.5)	1 (1.5)	68
≤10	31 (86.1)	3 (8.3)	2 (5.6)	-	36
INR					
≤1.5	173 (85.6)	23 (11.4)	4 (2.0)	2 (1.0)	202
1.5-2.0	41 (83.7)	8 (16.3)	-	-	49
2.0-2.5	11 (84.6)	2 (15.4)	-	-	13
2.5-3.0	8 (88.9)	1 (11.1)	-	-	9
>3.0	6 (60.0)	4 (40.0)	-	-	10
APTT (sec)					
≤30	75 (89.2)	10 (11.5)	2 (2.3)	-	87
31-45	105 (85.4)	15 (12.2)	1 (0.8)	2 (1.6)	123
46-60	37 (88.1)	5 (11.9)	-	-	42
61-75	13 (68.4)	5 (26.3)	1 (5.3)	-	19
>75	9 (81.8)	2 (18.2)	-	-	11

CVC = Central venous catheter; INR = International normalized ratio; APTT = Activated partial thromboplastin time | All numbers are presented as n(%), as percentages within each cohort of platelet count, INR or APTT

Appendix 11. Sensitivity analysis (logistic regression)

	Odds ratio	95% CI	df	p-value
Intercept	0.20	0.02 - 1.85	32	0.17
Coagulopathy	0.98	0.40 – 2.41	144	0.96
Platelet count	0.99	0.96 - 1.02	204	0.40
Fibrinogen	0.93	0.69 - 1.26	16	0.66
ICU admission diagnosis				
Sepsis	(ref)	(ref)	(ref)	(ref)
Pulmonary	0.75	0.25 – 2.26	238	0.61
Cardiac	0.67	0.05 – 8.90	186	0.76
Neurological	0.88	0.03 – 22.3	147	0.94
Routine post-cardiac surgery	0.60	0.06 – 6.36	258	0.67
Surgery (other)	0.26	0.04 – 1.0	205	0.13
Other	2.08	0.66 – 6.56	99	0.21
Haematological diagnosis				
None	(ref)	(ref)	(ref)	(ref)
AML	0.57	0.15-2.09	173	0.39
ALL	0.30	0.04-2.08	256	0.22
Lymphoma	0.74	0.20-2.68	205	0.65
Multiple myeloma	1.61	0.21-12.2	135	0.65
MDS	0.90	0.12-6.55	224	0.92
Other	0.98	0.25-3.83	209	0.98
Bleeding elsewhere	3.15	1.35-7.35	248	0.008 **
Catheter type				
Regular CVC	(ref)	(ref)	(ref)	(ref)
CVVH catheter	0.57	0.25-1.30	250	0.18
Number of tries	1.30	0.80-2.12	123	0.29
Arterial puncture	5.09	0.67-38.7	27	0.13
Clotting factors	2.11	0.64-6.92	242	0.22
Operator specialty				
Anesthesiology	(ref)	(ref)	(ref)	(ref)
Internal medicine	0.55	0.16-1.91	200	0.35
Neurology	0.01	0.00-inf	262	0.99
Cardiology	0.16	0.01-1.89	45	0.15
Other	0.87	0.23-3.33	177	0.23

ICU = Intensive Care Unit; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoid leukemia; MDS = Myelodysplastic Syndrome; CVC = Central Venous Catheter; CVVH = Continuous Veno-Venous Hemofiltration
 | * p<0.05, ** p<0.01, *** p<0.001

Appendix 12. Sensitivity analysis (raw INR & APTT)

	Odds ratio	95% CI	df	p-value	
Intercept	0.20	0.02 – 2.66	26	0.24	
INR	1.58	0.81 – 3.08	187	0.18	
APTT	0.99	0.96-1.01	201	0.31	
Platelet count	0.98	0.95 - 1.02	202	0.33	
Fibrinogen	0.94	0.69 - 1.29	15	0.73	
ICU admission diagnosis					
Sepsis	(ref)	(ref)	(ref)	(ref)	
Pulmonary	0.69	0.23 – 2.15	227	0.53	
Cardiac	0.41	0.02 – 6.74	208	0.53	
Neurological	0.86	0.03- 21.8	156	0.93	
Routine post-cardiac surgery	0.62	0.06 – 6.61	256	0.70	
Surgery (other)	0.19	0.03 – 1.23	207	0.08	
Other	1.94	0.60 – 6.31	90	0.27	
Haematological diagnosis					
None	(ref)	(ref)	(ref)	(ref)	
AML	0.53	0.14-2.06	122	0.36	
ALL	0.20	0.02-1.86	222	0.16	
Lymphoma	0.83	0.22-3.09	175	0.79	
Multiple myeloma	1.71	0.23-12.9	232	0.60	
MDS	0.85	0.12-6.34	200	0.88	
Other	0.98	0.25-3.80	204	0.98	
Bleeding elsewhere	3.23	1.37-7.61	246	0.008	**
Catheter type					
Regular CVC	(ref)	(ref)	(ref)	(ref)	
CVVH catheter	0.60	0.26-1.38	250	0.23	
Number of tries	1.23	0.75-2.04	123	0.41	
Arterial puncture	5.59	0.70-44.5	28	0.11	
Clotting factors	2.15	0.64-7.20	249	0.22	
Operator specialty					
Anesthesiology	(ref)	(ref)	(ref)	(ref)	
Internal medicine	0.53	0.15-1.88	209	0.33	
Neurology	0.01	0.00-inf	261	0.99	
Cardiology	0.16	0.01-1.83	50	0.16	
Other	0.90	0.23-3.47	169	0.88	

INR = International Normalised Ratio; APTT = Activated Partial Thromboplastin Time; ICU = Intensive Care Unit; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoid leukemia; MDS = Myelodysplastic Syndrome; CVC = Central Venous Catheter; CVVH = Continuous Veno-Venous Hemofiltration | * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix 13. Baseline characteristics by platelet transfusion

	Total	No transfusion	Transfusion	
N	289	172	117	
Patient demographics				
Female, n(%)	121 (41.9)	73 (42.4)	48 (41.0)	
Age (years), median (iqr)	57 (43-64)	57 (44-65)	57 (43-63)	
BMI (kg/m ²), median (iqr)	25 (22-30)	25 (23-29)	25 (22-29)	
Disease severity				
SOFA-score, mean (sd)	12.8 (4.3)	12.3 (4.2)	13.5 (4.4)	*
CP-score, median (iqr)	9 (7-10)	8 (7-10)	9 (7-10)	
CCI, median (iqr)	3 (2-5)	3 (2-5)	3 (2-5)	
ISTH DIC-score, median (iqr)	7 (6-7)	7 (6-7)	7 (6-7)	
Temperature (°C), mean(sd)	37.2 (1.2)	37.2 (1.2)	37.2 (1.3)	
Concurrent bleeding elsewhere, n(%)	151 (52.2)	86 (50.0)	65 (55.6)	
Laboratory values				
Platelets (x 10 ⁹ /L) , median (iqr)	27 (16-38)	32 (21-43)	19 (9-29)	***
Hemoglobin (mmol/L), median (iqr)	5.1 (4.6-5.9)	5.2 (4.7-6.0)	4.9 (4.4-5.6)	**
INR, median (iqr)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.2-1.5)	
aPTT (sec) , median (iqr)	35 (29-46)	36 (30-46)	34 (29-44)	
Fibrinogen (g/L), median (iqr)	3.4 (1.8-5.5)	3.2 (1.7-5.1)	3.7 (1.9-5.9)	
D-dimer (g/L), median (iqr)	9.8 (3.5-20.5)	10.5 (5.3-21.4)	9.5 (2.8-20.0)	
Diagnoses				
ICU admission diagnosis, n(%)				
Sepsis	132 (45.7)	72 (41.9)	60 (51.3)	
Pulmonary	54 (18.7)	30 (17.4)	24 (20.5)	
Cardiac	13 (4.5)	6 (3.5)	7 (6.0)	
Routine post-cardiac surgery	15 (5.2)	10 (5.8)	5 (4.3)	
Surgery (other)	28 (9.7)	19 (11.0)	9 (7.7)	
Other	47 (16.3)	35 (20.4)	12 (10.3)	
Haematological diagnosis, n(%)				
Any	149 (51.6)	75 (43.6)	74 (63.2)	***
AML	47 (16.3)	20 (11.6)	27 (23.1)	
ALL	18 (6.2)	3 (1.7)	15 (12.8)	
Lymphoma	40 (13.8)	25 (14.5)	15 (12.8)	
Multiple myeloma	10 (3.5)	9 (5.2)	1 (0.9)	
MDS	12 (4.2)	3 (1.7)	9 (7.7)	
Other	22 (7.6)	15 (8.7)	7 (6.0)	
CVC placement				
US-guided, n(%)	212 (99.5)	114 (99.1)	98 (100.0)	
Number of tries, median (iqr)	1 (1-1)	1 (1-1)	1 (1-1)	
CVVH catheter, n(%)	113 (39.4)	70 (41.2)	43 (36.8)	
Number of lumens, median (iqr)	3 (2-3)	3 (2-3)	3 (2-3)	
Insertion site, n(%)				
Internal jugular vein	167 (58.2)	90 (52.6)	77 (66.4)	*
Subclavian vein	8 (2.8)	7 (4.1)	1 (0.9)	
Femoral vein	112 (39.0)	74 (43.3)	38 (32.8)	
Operator specialty, n(%)				
Anaesthesiology	123 (64.4)	67 (63.8)	56 (65.1)	

Internal medicine	32 (16.8)	16 (15.2)	16 (18.6)
Neurology	16 (8.4)	7(6.7)	9 (10.5)
Cardiology	10 (5.2)	6 (5.7)	4 (4.7)
Other	10 (5.2)	9 (8.6)	1 (1.2)
Concurrent therapies†			
Unfractionated heparin, n(%)	17 (5.9)	11 (6.4)	6 (5.1)
Low molecular weight heparin, n(%)			
None	104 (36.1)	64 (37.4)	40 (34.2)
Normal prophylactic dose	169 (58.7)	96 (56.1)	73 (62.4)
Double prophylactic dose	8 (2.8)	4 (2.3)	4 (3.4)
Therapeutic dose	7 (2.4)	7 (4.1)	0 (0.0)
Coumarin or DOAC, n(%)	6 (2.1)	5 (2.9)	1 (0.9)
Platelet aggregation inhibitor, n(%)	16 (5.5)	13 (7.6)	3 (2.6)
Tranexemic acid, n(%)	50 (17.3)	29 (16.9)	21 (17.9)
Clotting factors, n(%)	41 (14.2)	23 (13.4)	18 (15.4)
Vitamin K, n(%)	32 (11.1)	18 (10.5)	14 (12.0)

*BMI = Body Mass Index; SOFA = Sequential Organ Failure Assessment; CP = Child-Pugh; CCI = Charlson Comorbidity Index; ISTH = International Society on Thrombosis and Haemostasis; DIC = Disseminated intravascular coagulation; INR = International Normalised Ratio; aPTT = activated Partial Thromboplastin Time; ICU = Intensive Care Unit; AML = Acute Myeloid Leukemia; ALL = Acute Lymphoid leukemia; MDS = Myelodysplastic Syndrome; CVC = Central Venous Catheter; US = ultrasound; CVVH = Continuous Veno-Venous Hemofiltration; DOAC = Direct Oral Anticoagulants | * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ | † Unfractionated heparin was not counted if it was stopped >1 hour prior to CVC placement, other (anti-) coagulants were counted if administered <1 week prior to CVC placement.*

Appendix 14. Platelet count increment after transfusion of 1 unit platelet concentrate

	Total	Abnormal coagulation	Normal coagulation
N	108	41	67
Platelet count pretransfusion, median (iqr)	19 (9-29)	20 (11-29)	19 (10-28)
Platelet count posttransfusion, median (iqr)	39 (25-60)	34 (25-64)	43 (30-56)
Platelet count increment, median (iqr)	20 (10-34)	20 (10-34)	20 (8-32)
Corrected count increment, median (iqr)	14 (8-25)	15 (8-24)	14 (8-26)

Posttransfusion platelet counts were obtained either before central venous catheter (CVC) placement or within 2 hours afterwards, so within 8 hours after platelet transfusion. Only patients with both pre- and posttransfusion platelet counts and a platelet transfusion within 6 hours before CVC placement are represented in this table.